REMARKS

The instant application was filed on December 18, 2001, as a continuation-in-part application of U.S. Patent Application No. 10/045,816, filed on October 25, 2001, with 61 claims. Of the original claims, claims 1-37 were composition claims directed to a dosage form and claims 38-61 were method claims directed to the delivery of a dosage form to the upper gastrointestinal tract. On May 23, 2003, the Office mailed a Restriction Requirement requiring: (i) election between the composition and method claims, and (ii) election of one species from each of the following compounds: a polymer (claims 21-24); an active agent (claims 26-30); a vesicle (claims 32-34) or no vesicle for containing the active agent (claim 1); and a dosage form that is either a tablet (claim 36) or a capsule (claim 37). On June 16, 2003, applicants filed a response electing the composition claims and the following species: poly(ethylene oxide); ciproflaxin; no vesicle; and a tablet. The Office Action under reply is the first Office Action on the merits for this application.

In the Office Action under reply, claims 1-28 and 36 were examined; claims 29-37 were withdrawn from consideration as drawn to non-elected species; and claims 38-61 were withdrawn from consideration as directed to a non-elected invention. The pending claims were subject to one rejection, an anticipation rejection over Wong et al. (U.S. Patent No. 6,120,803).

Further to the Examiner's statement that the Information Disclosure Statements of December 18, 2001, and April 4, 2003, were not considered because the references could not be located in the designated prior art storage area, applicants advise the Examiner that resubmissions of these two Information Disclosure Statements have been filed concurrently with this response.

THE CLAIM AMENDMENTS

With the present amendment, claim 1 has been amended to more clearly define the process for determining an optimal rate of release of the active agent from the dosage form, which is by taking the ratio of the erosion rate ER obtained *in vitro* for the dosage form to the dissolution rate DR obtained *in vitro* for the dosage form such that the ratio of ER to DR in the dosage form is approximately 1.2:1 to approximately 5:1. The amendment to claim 1 does not recite any previously unclaimed subject matter; nevertheless, support for the recitation of the ER to DR ratio is found, *inter alia*, in the specification at page 14, lines 8-9, and page 15, lines 2-9. New claims 62 to 65 further define claim 1 by reciting that the ER and DR are determined using disintegration and dissolution tests with USP disintegration and dissolutions equipment, respectively. The subject matter of claims 62 and 65 was previously recited in claim 1.

In addition to the foregoing, new independent claim 66 recites that the dosage form is a tablet with at least two layers wherein at least one of the at least two layers contains the active agent and is comprised of a polymer that is erodible. New claims 67 to 73 recite the different ways that the at least two layers may be configured within the context of the claimed dosage form. Support for the subject matter of claims 64-71 is found in the specification at page 6, lines 3-10, Example 2, pages 48-49; Example 3, page 50; and Figures 5 and 6.

Lastly, method claims 38-61 have been canceled as a result of the restriction requirement for this application. This cancellation is made without prejudice and as such applicants reserve the right to file one or more divisional applications on the canceled subject matter.

No new matter has been added to the application with any of the claim amendments set forth herein.

CLAIM REJECTION – 35 U.S.C. § 102(b)

Claims 1-28 and 36 stand rejected under 35 U.S.C. § 102(b) as anticipated by Wong et al. (U.S. Patent No. 6,120,803). This rejection is respectfully traversed.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently, in a single prior art reference. *Minn. Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1565, 24 USPQ2d 1321, 1326 (Fed. Cir. 1992). It is well-established that a product-by-process claim is a product claim that defines the claimed product in terms of the process by which it is made. *See, In re Luck*, 476 F.2d 650, 177 USPQ 523 (CCPA 1973); *In re Pilkington*, 411 F.2d 1345, 162 USPQ 145 (CCPA 1969); *In re Steppan*, 394 F.2d 1013, 156 USPQ 143 (CCPA 1967). The structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product. *See, e.g., In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979).

As recited in claim 1, the present invention is directed to a sustained release oral dosage form for delivering a pharmacologically active agent to the stomach, duodenum, and upper small intestine of a patient with restricted delivery to the lower intestinal tract and colon, the dosage form comprising a therapeutically effective amount of the pharmacologically active agent incorporated in a matrix of at least one biocompatible, hydrophilic polymer that: (a) swells in the presence of water in gastric fluid such that the size of the dosage form is sufficiently increased to provide gastric retention of the dosage form in the stomach of a patient in whom the fed mode has been induced; and (b) gradually erodes within the

gastrointestinal tract over a determinable time period, wherein the optimal rate of sustained release of the dosage form is determined by taking the ratio of the erosion rate ER obtained *in vitro* for the dosage form using USP disintegration test equipment to the dissolution rate DR obtained *in vitro* for the dosage form using USP dissolution test equipment such that the ratio of ER to DR in the dosage form is approximately 1.2:1 to approximately 5:1.

As explained on pages 18-19 of the specification, erosion initiates simultaneously with the swelling process upon contact of the surface of the dosage form with gastric fluid. Erosion reflects the dissolution of the polymer beyond the polymer gel-interface where the polymer has become sufficiently dilute that it can be transported away from the dosage form by diffusion or convection. While swelling and erosion occur at the same time, it is preferred within the context of the invention, that the drug release is erosion-controlled, i.e., the selected polymer should be such that complete drug release occurs primarily as a result of erosion rather than swelling and dissolution. Preferred dosage forms of the claimed invention have an erosion rate that slightly faster than the swelling rate, such that drug release from the dosage form is primarily controlled by polymer erosion rather than by polymer swelling (page 14, lines 26-28).

The process of the claimed invention permits for the manufacture of an optimized dosage form where the erosion rate exceeds the swelling rate by a factor of 1.2:1 to 5:1. At page 6 of the specification, it is explained that the term "erosion rate" is synonymous with the term "disintegration rate" (line 23). Similarly, at page 7 of the specification, it is explained that the term "swelling rate" is synonymous with the term "dissolution rate" (page 7, lines 9-10). As explained on page 5 of the specification, the optimization of the ER to DR ratio may be controlled by: (i) adjusting the size and or shape of the dosage form; (ii) selecting matrix polymers having particular swelling and erosion rates; (iii) increasing or decreasing drug loading; and/or (iv) using additives such as disintegrants and solubilizers (lines 9-12). For example, the rate of diffusion of dissolved active agent out of the matrix (the DR) can be slowed relative to the rate at which the active agent is released via polymer erosion (the ER) by increasing the volume fraction of drug and selecting a polymer that will erode faster than it will swell (lines 12-15).

Wong et al. teaches devices for delivering an active agent to the gastric environment over a prolonged period of time, i.e., 4 to 24 hours (col. 4, ll. 59-61 and 65). Wong et al. states that such devices should exhibit *a combination of flexibility and rigidity* so as not to be expelled from the stomach to the pyloric sphincter under fed or fasting conditions (col. 4, l. 65 to col. 5, l. 1). Specifically, in one embodiment, Wong et al. teaches an active agent dosage form for the prolonged delivery of an active agent to the stomach of a human or other animal wherein the active agent is in a polymeric matrix formed of a mixture of a swellable water soluble polymer that expands when in contact with fluids in the gastric

environment and a hydroattractant that is preferably water insoluble (col. 5, ll. 10-16). The matrix is formed *with a rigid or semi-rigid segment* in which swelling of the hydrogel is constrained to provide a rigid or semi-rigid section in the dosage form that facilitates the dosage form remaining in the stomach of a subject over a prolonged period of time (col. 5, ll. 16-21). The rigid or semi-rigid section of the dosage form comprises one or more insoluble materials, typically exhibiting low water impermeability and formed as a band circumscribing a portion of the polymer matrix (col. 5, ll. 21-27).

Wong et al. explains that *the insoluble material or band(s) prolongs the period of time in which the polymer matrix retains its integrity in an expanded state and increases the residence time of the dosage form in the stomach* (col. 5, ll. 28-32). The band limits the transport of fluid into the portion of the polymer matrix that it surrounds and provides the polymer matrix with enough rigidity to permit the dosage form to resist the compressive force of the contractions of the stomach during the housekeeping phase so that the dosage form remains in the stomach for a prolonged period of time (col. 5, ll. 32-38). As the dosage form erodes in the stomach or as active agent diffuses from the matrix, active agent is released and either absorbed by the stomach or passed from the stomach to the small intestine (col. 5, ll. 38-41).

As an alternative to the bands, Wong et al. teaches that *the dosage form may be formed as a swellable polymer matrix attached to a separate active agent reservoir, from which the active agent is delivered* (col. 6, ll. 59-62). In this embodiment, the polymer matrix is formed as a tube or annular ring and placed about the reservoir, such that swelling of the polymer retains the active agent within the tube or ring to promote retention of the dosage form in the stomach over a prolonged period of time (col. 6, l. 62 to col. 7, l. 1). The active agent reservoir contributes to the rigidity of the dosage form such that along with the gel properties of the polymer matrix, the dosage form is retained in the stomach for a prolonged period of time (col. 7, l. 5-9).

Referring to the Figures, Wong et al. provides that Fig. 1A presents the device in preparation prior to application of the insoluble material or band 15 that is shown in Fig. 1B. The active agent 12 the figures is found within the polymer matrix 11, which is formed of a combination of a swellable, high molecular weight, water-soluble polymer and a hydroattractant (col. 9, ll. 59-67). Polyethylene oxide is disclosed as one polymer and water-insoluble cellulose polymers are disclosed as representative hydroattractants (col. 10, ll. 10-18; col. 10, l. 63-67). The dosage form of Wong et al. with one insoluble band is seen at reference number 15 in Figs. 1B, 2, 3A, and 3B. As explained by Wong et al., the band typically exhibits low water permeability and prevents that portion of the polymer matrix that it surrounds from imbibing fluid, thus substantially limiting any swelling of the polymer matrix at that location (col. 11, ll. 44-48). At Figs. 4A-4D, the dosage form with two insoluble bands is depicted: Fig. 4A shows the

dosage form in its initial configuration; Fig. 4B shows the dosage form in its swelled configuration; Fig. 4C shows the dosage form after it has been eroded by gastric fluid; and Fig. 4D shows the late stage of the erosion where the dosage form separates into two pieces and is expelled from the stomach (col. 11, l. 60 to col. 12, l. 8). Figures 5-7 show the reservoir as it is used with the swellable polymer matrix.

By studying the disclosure of the claimed invention against that of Wong et al., it is evident that where the present invention uses the ratio of the ER and DR to produce a dosage form that swells and erodes at an *optimized* rate, Wong et al. uses an insoluble band or a reservoir to *control* the swelling and erosion of the dosage form disclosed therein. Thus, unlike Wong et al., the claimed invention utilizes the process of taking the ER to DR ratio to impart a distinctive structural characteristic to the claimed oral dosage form. *See*, *In re Garnero*, *supra*. By contrast, because Wong et al. provides no process by which to optimize the disclosed dosage form, the insoluble band and reservoir serve the purpose of controlling the dissolution and disintegration of an unoptimized dosage form. Accordingly, because Wong et al. does ***not*** teach or suggest that the swelling or erosion rate of the claimed dosage form may be optimized to produce a dosage form with structural integrity without the use of an external band or reservoir, it follows that Wong et al. does not anticipate the claimed invention.

Turning to new claims 64-71, Wong et al. does not anticipate or render the claimed invention obvious because Wong et al. does ***not*** teach or suggest a dosage form that is a tablet with at least two layers wherein at least one of the at least two layers contains the active agent and is comprised of a polymer that is erodible (claim 64).

CONCLUSION

With the present amendment, the Examiner's sole rejection has been addressed and overcome. Accordingly, upon reversal of the rejection, this application will be in condition for allowance. In light of the foregoing, applicants respectfully request passage of this application to issue.

If the Examiner has any questions regarding this response, he is welcome to contact the undersigned attorney at 650-330-4913 or at canaan@reedpatent.com.

Respectfully submitted,

By: _____
Karen Canaan
Registration No. 42,382

REED & EBERLE LLP
800 Menlo Avenue, Suite 210
Menlo Park, California 94025
(650) 330-0900 Telephone
(650) 330-0980 Facsimile